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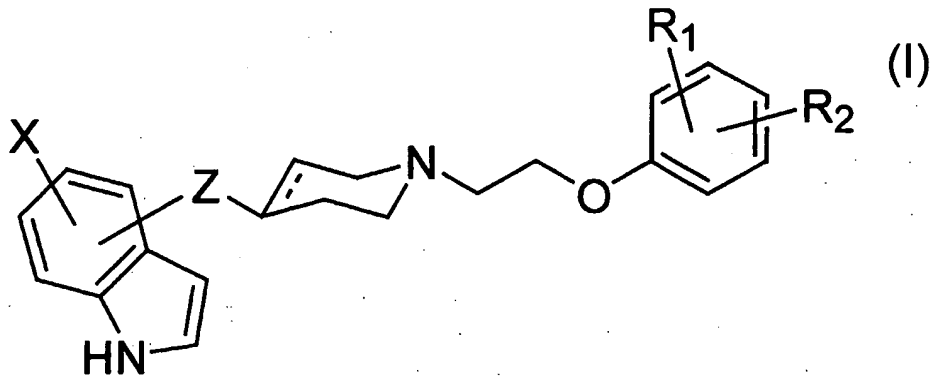
(54) Title: ARYLOXY PIPERIDINYL DERIVATIVES FOR THE TREATMENT OF DEPRESSION




(57) Abstract: This invention provides compounds useful in treating serotonin-related central nervous system disorders, including anxiety, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, sleep disorders, sexual dysfunction, alcohol and drug addiction, Alzheimer's disease, Parkinson's disease, obesity and migraine, the compounds having the general formula: wherein: $R_1$ and $R_2$ may each be H or an alkyl or alkoxy group; or $R_1$ and $R_2$ may be concatenated to form a bicyclic ring system with the phenyl ring to which they are bound; X is selected from hydrogen, halogen, cyano, $C_1$-$C_6$ alkoxy; Z is $(CH_2)n$ or carbonyl; n is 0, 1 or 2; the dashed line indicates an optional double bond; or a pharmaceutically acceptable salt thereof.

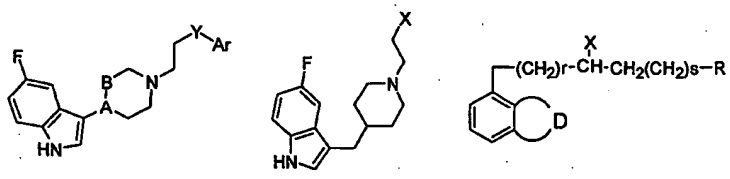
WO 02/48105 A2

# ARYLOXY PIPERIDINYL DERIVATIVES FOR THE TREATMENT OF DEPRESSION

This invention relates to new aryloxy indole derivatives as pharmaceuticals which are useful for the treatment in mammals of diseases affected by disorders of the serotonin-affected neurological systems, such as depression, anxiety, panic disorder, obsessive-compulsive disorder, sleep disorders, sexual dysfunction, alcohol and drug, addiction, Alzheimer's disease, Parkinson's disease, obesity and migraine, as well as methods of enhancing cognition.

## BACKGROUND OF THE INVENTION

EP 0714894 A1 discloses the preparation of compounds of formula II as new 5-$HT_{1f}$ agonist for the treatment of migraine headaches. EP 429341 A2 claims compounds of formula III as having serotonin transporter activity. A recent publication by Malleron et al. was also reported based around formula I [J. Med. Chem. 36, 1194 (1993)]. EP 722941 A2 discloses compounds having effects on serotonin-related systems of formula IV.




II III IV

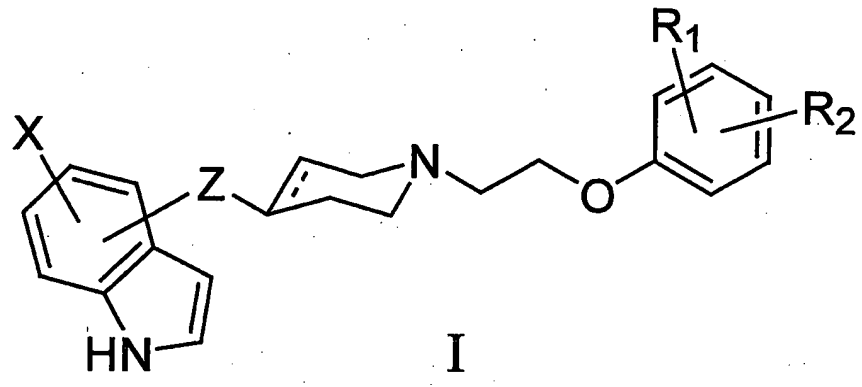
Pharmaceuticals which enhance serotonergic neurotransmission are of useful benefit for the treatment of many psychiatric disorders, including depression and anxiety. The first generation of non-selective serotonin-affecting drugs operated through a variety of physiological functions which endowed them with several side effect liabilities. The more currently prescribed drugs, the selective serotonin (5-HT) reuptake inhibitors (SSRIs), act predominately by inhibiting 5-HT, which is released

at the synapses, from being actively removed from the synaptic cleft via a presynaptic serotonin transport carrier. Since SSRIs require several weeks before they exert their full therapeutic effect, this 5-HT blockade mechanism *per se* cannot account for their therapeutic activity. It is speculated that this two week induction which occurs before a full antidepressant effect is observed, is due to the involvement of the 5-$HT_{1A}$ autoreceptors which suppress the firing activity of 5-HT neuron, causing a dampening of the therapeutic effect. Studies suggest that after several weeks of SSRI administration, a desensitization of the 5-HT autoreceptors occurs allowing a full antidepressant effect in most patients. Recent studies by Artigas et al. (Trends Neurosci., 1996, 19, 378-383) suggest a combination of 5-$HT_{1A}$ activity and inhibition of 5-HT uptake within a single molecular entity can achieve a more robust and fast-acting antidepressant effect.

The present invention relates to a new class of molecules which have the ability to act at the 5-$HT_{1A}$ autoreceptors and concomitantly with the 5-HT transporter. Such compounds are therefore potentially useful for the treatment of depression as well as other serotonin disorders.

## SUMMARY OF INVENTION

The compounds of this invention are aryloxy piperidinyl indoles represented by Formula I:




I

wherein:

$R_1$ and $R_2$ may each be hydrogen or an alkyl of from 1 to 6 carbon atoms or an alkoxy group of from 1 to 6 carbon atoms; or

$R_1$ and $R_2$ may be concatenated to comprise another ring system wherein the ring contains a total of 5-7 ring members;

X is selected from hydrogen, halogen, cyano, $C_1$–$C_6$ alkoxy;

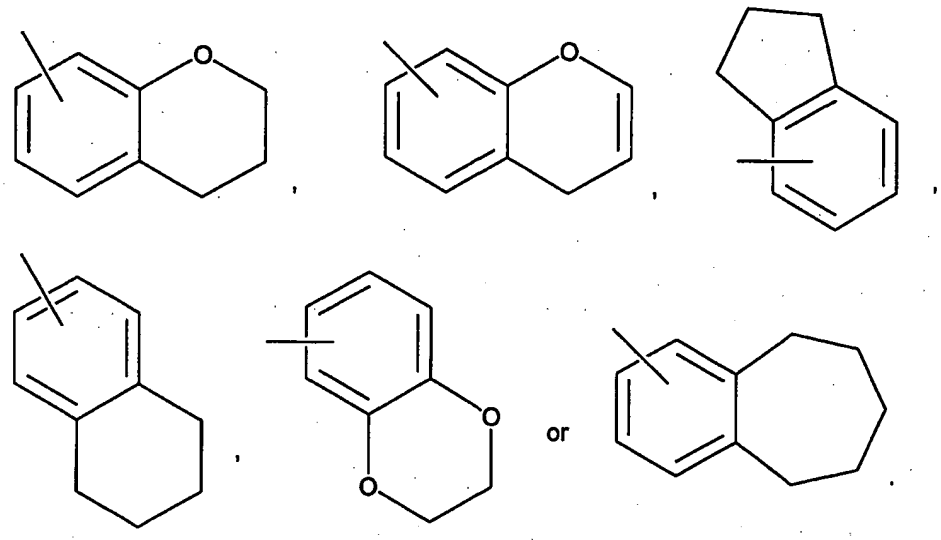
Z is $(CH_2)n$ or carbonyl;

n is 0, 1 or 2;

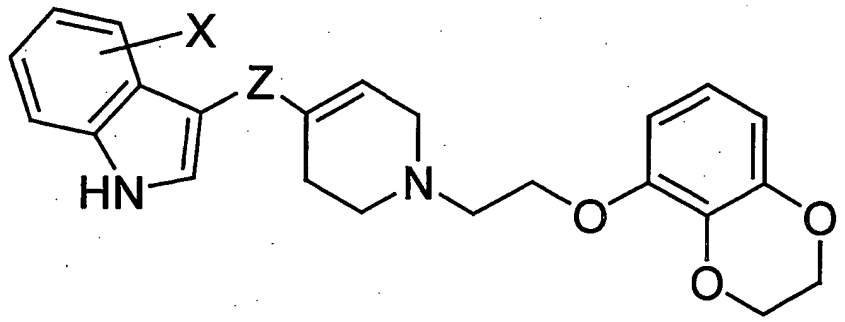
the dashed line indicates an optional double bond;

or a pharmaceutically acceptable salt thereof.

Ring systems formed by the concatenation of $R_1$ and $R_2$ are understood to contain the carbon or oxygen atoms of the $R_1$ and $R_2$ groups and can being saturated or unsaturated, including fused alkyl, pyran, or dioxan ring systems. With the phenyl ring to which they are bound, the concatenated rings can form the moieties:



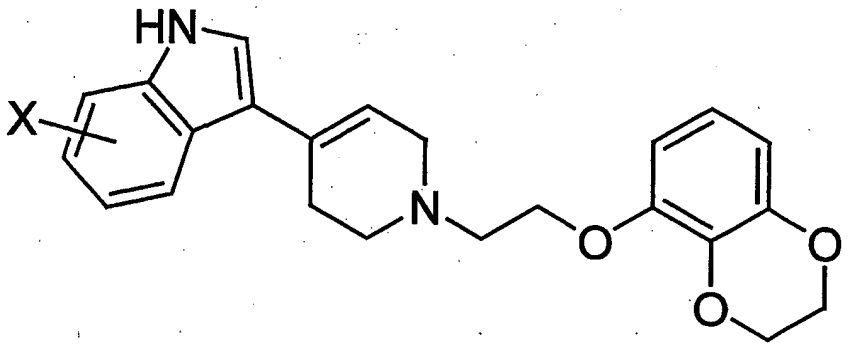

One group of compounds of this invention comprises compounds of the formula:




wherein X is selected from H, halogen, cyano, $C_1$–$C_6$ alkoxy; Z is $(CH_2)n$ or carbonyl;

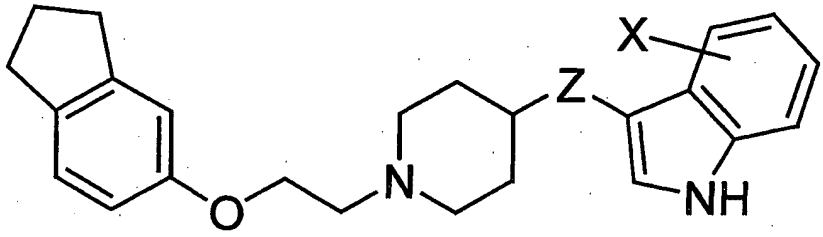
and n is 0, 1 or 2; or a pharmaceutically acceptable salt thereof.

Another group of compounds of this invention comprises those of the formula:




wherein X is H, halogen, cyano, $C_1$–$C_6$ alkoxy, or a pharmaceutically acceptable salt thereof.

A further group of compounds of this invention, and pharmaceutically acceptable salts thereof, are represented by the formula:




wherein X and Z are as defined above.

In the formulae disclosed herein:

$R_2$, $R_3$ and $R_4$ may each independently represent hydrogen, alkyl of 1 to 3 carbon atoms, chlorine or fluorine.

Examples of X are hydrogen, fluorine, chlorine, CN and methoxy, e.g., in the 5- or 6- position.

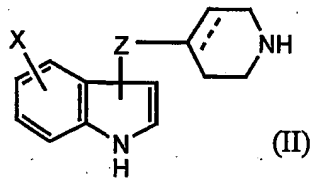
Z may be for example a bond (i.e., n is 0) or -$CH_2$- (i.e., n is 1). Z may be bonded to the indole ring for example in the 3-position.

Examples of $R_1$ and $R_2$ are independently hydrogen, alkyl of 1 to 3 carbon atoms (e.g. methyl) and alkoxy of 1 to 3 carbon atoms (e.g. methoxy). When concatenated together examples of $R_1$ and $R_2$ are as illustrated above.

The compounds of this Formula I also may be used in the form of a pharmaceutically acceptable acid addition salt having the utility of the free base. Such salts, prepared by methods well known to the art are formed with both inorganic or organic acids, for example: fumaric, maleic, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, oxalic, propionic, tartaric, salicyclic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene-sulfonic, hydrochloric hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

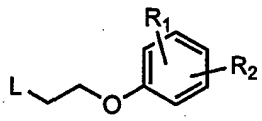
This invention also provides processes for preparing the compounds of formula (I) which processes comprise:

a) reacting a compound of formula




(II)

wherein X and Z are as defined above, with a compound of formula:




wherein $R_1$ and $R_2$ are as defined herein and L is a leaving group,

or

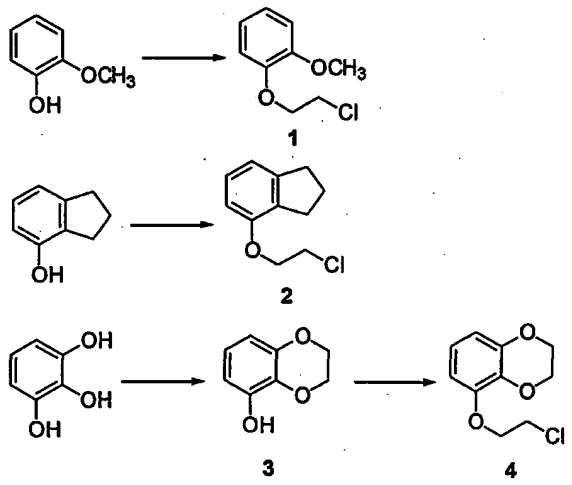
b) converting a basic compound of formula I to a an acid addition salt or vice versa

or

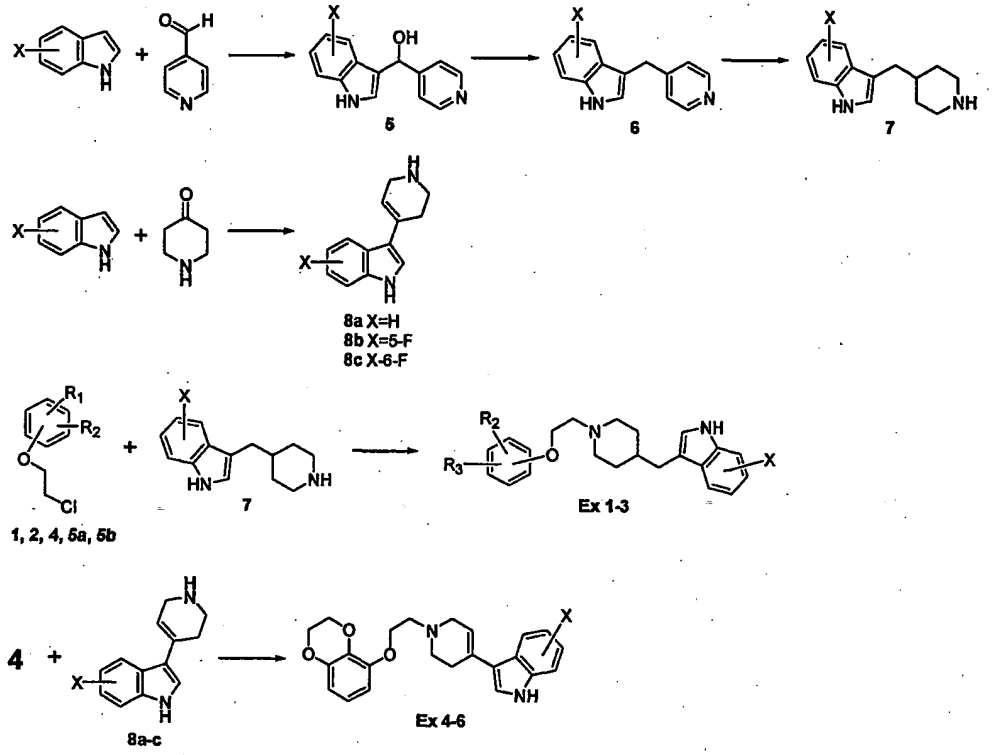
c) isolating an isomer of a compound of formula I from a mixture of isomers.

In detail the compounds of Formula I may be generally prepared by the overall sequence indicated in Scheme 1 and 2 as follows:

**Scheme 1**



**Scheme 2**




The following examples for preparation of intermediates and invention compounds are included for illustrative purposes and are not to be construed as limiting to this disclosure in any way. Those skilled in the art of organic synthesis may be aware of still other synthetic routes to the invention compounds. The reagents and intermediates used herein are either commercially available or prepared according to standard literature procedures.

## Intermediate 1

**1-(2-Chloroethoxy)-2-methoxybenzene.**

To a solution of 2-methoxyphenol (14.4 g, 116 mmol) in 2-butanone (200 mL) was added bromochloroethane (69.0 g, 480 mmol) followed by the addition of

potassium carbonate (40.0 g, 280 mmol). The reaction mixture was mechanically stirred and heated to reflux for 24 h, then cooled to room temperature. The solids were filtered off and the solvent was removed under vacuum. The residue was dissolved in diethyl ether and washed with 10% of NaOH, dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by silica gel column chromatography (25 % EtOAc/hexane) afforded 7.55 g (35%) of a solid: mp 36-38 °C (Lit.[2] 41-43 °C); $^1$H NMR (DMSO, 400 MHz), δ 3.75 (s, 3H), 3.91 (dd, 2H), 4.20 (dd, 2H), 6.86-6.99 (m, 4H); MS (El) m/z 186 ($M^+$).

**Intermediate 2**

**5-(2-Chloroethoxy)-indane.**

Replacing 2-methoxyphenol with commercially available 5-hydroxyindane and using the above procedure afforded the title compound in 43 % yield as a white solid: mp 45-46 °C.

Elemental Analysis Calcd for $C_{11}H_{13}OCl$

Theory: C, 67.18; H, 6.66

Found: C, 67.03; H, 6.57

**Intermediate 3**

**5-Hydroxy-(2,3)-dihydrobenzo[1,4]dioxan**

Pyrogallol (5 g, 0.04 mmol) was dissolved in 2-butanone (600 mL) to which potassium carbonate (1.82 g, 0.013 mol) was added. The mixture was stirred at reflux while 1,2-dibromoethane (2.48 g, 1.14 mL, 0.013 mol) was slowly added drop wise. The reaction was allowed to stir overnight and then cooled to room temperature. The mixture was poured into water (100 mL) and extracted with methylene chloride (200 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and the

solvent removed under vacuum. Chromatography (5% methanol-methylene chloride) afforded 2.74 g (45 %) of a clear oil.

**Intermediate 4**

**5-(2-Chloroethoxy)-(2,3)-dihydrobenzo[1,4]dioxan**

To solution of 5-hydroxy benzodioxan (1 g, 6.5 mmol) and 2-chloroethanol (.79 g, 9.9 mmol), triphenylphosphine (2.6 g, 9.9 mmol) in THF (50 mL) was slowly added diisopropylazidodicarbimide (DIAD) (2.0 g, 9.8 mmol). After 2 h, another 1.5 eq of triphenylphosphine, DIAD, and 2-chloroethanol was added and the reaction stirred for another 2 h. The reaction mixture was poured into water (100 mL), and extracted with methylene chloride (100 mL). The organic layer was separated and dried over anhydrous magnesium sulfate, filtered, and the solvent removed under vacuum. Chromatography (ethyl acetate-hexane: 1:4) afforded 1.7 g (76 %) of a white solid: mp 70.5-72.5 °C.

Elemental Analysis for $C_{10}H_{11}ClO_3$

Theory: C, 55.96; H, 5.17

Found: C, 55.57; H, 5.20

**Intermediate 5**

**(5-Fluoro-1*H*-indol-3-yl)-pyridin-4-yl-methanol.**

To a stirred solution of 5-fluoroindole (3.10 g, 23.0 mmol) in methanol (10.0 mL) was added 4-pyridinecarboxaldehyde (2.20 mL, 23.0 mmol), followed by addition of NaOH (2.5 mL, 50%) at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for 3 h, followed by the addition of water (10.0 mL). The precipitate was collected by filtration and dried under vacuum to afford 5.2 g (93%) of a light yellow solid: mp 171-173 °C; $^1$H NMR

(DMSO, 400 MHz), δ 5.85 (d, 1H), 5.93 (d, 1H), 6.86-7.34 (m, 4H), 7.43 (dd, 2H), 8.48 (dd, 2H), 11.09 (br s, 1H); MS (El) m/z 242 ($M^+$); HRMS calcd for $C_{14}H_{12}FN_2O$ [M+H] 243.09337, found 243.09576.

**Intermediate 6**

**5-Fluoro-3-[(4-pyridinyl)methyl]-1*H*-indole**

To a suspension of (5-fluoro-1*H*-indol-3-yl)-pyridin-4-yl-methanol (0.799 g, 3.3 mmol) in methylene chloride (13 mL) was added triethylsilane (0.60 mL, 3.7 mmol) followed by trifluoroacetic acid (2.85 mL, 37 mmol) at room temperature. After addition of trifluoroacetic acid, a clear black solution was obtained. The reaction mixture was stirred overnight and the solvent and excess trifluoroacetic acid was removed on a rotary evaporator. To the residue was added saturated $Na_2CO_3$ to adjust the pH>9. The aqueous layer was extracted with methylene chloride and the combined organic extracts was washed with water, brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel column chromatography (methylene chloride to methylene chloride/ethyl acetate to ethyl acetate, 100% to 50% to 100%) to give 0.56 g (75%) of a solid: mp 141-142 °C [(mp 149 °C ; previously reported in J. Med. Chem. 36, 1194 (1993)].

**Intermediate 7**

**5-Fluoro-3-[(4-piperidinly)methyl]-1*H*-indole**

This compound was prepared in 88% yield following the reported procedure (Malleron et.al, J. Med. Chem. 1993, 36, 1194).

**Intermediate 8a-c**

**(9c) 6-Fluoro-3-[1,2,3,6-tetrahydro-pyridin-4-yl]-1H-indole**

A solution of 6-fluoroindole (2 g, 15 mmol) and 4-piperidone (3 g, 19.6 mmol) in 2 N solution of KOH in MeOH (60 mL) was stirred at reflux for 72 h. The mixture was concentrated to ¼ volume, diluted with $H_2O$ and filtered affording 2.5 g (77%) as a pale yellow solid: mp 202-204 °C; MS (APCI) m/z 217 $[M+H]^+$.

**(9a) 3-[1,2,3,6-Tetrahydro-pyridin-4-yl]-1H-indole**

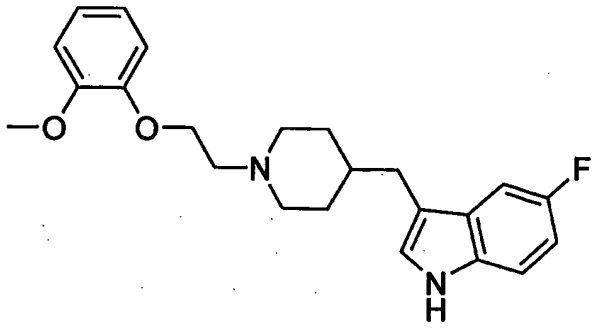
Replacing 6-fluoroindole with indole in the above procedure afforded the title compound % as a pale yellow solid.

**(9b) 5-Fluoro-3-[1,2,3,6-tetrahydro-pyridin-4-yl]-1H-indole**

Replacing 6-fluoroindole with 5-fluoroindole in the above procedure afforded the title compound % as a yellow solid.

**Example 1**

**5-Fluoro-3-{1-[2-(2-methoxyphenoxy)ethyl]-piperidin-4-ylmethyl}-1*H*-indole.**



To a solution of 5-fluoro-3-[(4-piperidinyl)methyl]-1*H*-indole (0.60 g, 2.59 mmol) [prepared according to Malleron et al., J. Med. Chem. 36, 1194 (1993)] in DMSO (20 mL) was added 1-(2-chloroethoxy)-2-methoxybenzene (0.48 g, 2.59 mmol) followed by addition sodium carbonate (0.55 g, 5.17 mmol) at room temperature. The reaction mixture was heated to 100 °C and stirred for 5 h. After cooling to room temperature, the reaction mixture was stirred overnight, and quenched with water, diluted with methylene chloride. The two layers were separated and the aqueous was extracted with methylene chloride. The combined organic extracts were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated. Purification by silica gel column chromatography (methylene chloride /methanol, 98/2) afforded 0.61 g (61%) of product. The free base (0.5 g, 1.31 mmol) was dissolved in ethanol, and precipitated with one equivalent of oxalic acid in ethanol to give the title compound (0.47 g, 76%) as the monooxalate, 0.25 hydrate: mp 91 °C; $^1$H NMR (DMSO, 400 MHz), δ 1.44-1.47 (m, 2H), 1.78-1.81 (m, 3H), 2.62 (d, 2H), 2.88-2.95 (m, 2H), 3.34-3.40 (m, 4H), 3.46-3.49 (m, 2H), 3.74 (s, 3H), 4.25 (t, 2H), 6.86-7.33 (m, 8H), 10.97 (br s, 1H); MS (El) m/z 382 ($M^+$).

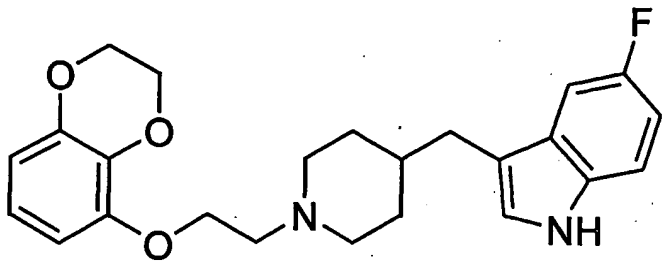
Elemental Analysis Calcd for $C_{23}H_{27}FN_2O_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$

Theory: C, 62.95; H, 6.23; N, 5.87.

Found: C, 63.00; H, 6.60; N, 5.47.

## Example 2

**5-Fluoro-3-{1-[2-(2,3-dihydrobenzo[1,4]dioxin-5-yloxy)ethyl]-piperidin-4-ylmethyl}-1*H*-indole.**



To a solution of 5-fluoro-3-[(4-piperidinyl)methyl]-1*H*-indole (0.35 g, 1.5 mmol) in DMSO (10 mL) was added 5-(2-chloroethoxy)-(2,3)-dihydrobenzo[1,4]dioxan (0.32 g, 1.5 mmol) followed by addition of triethylamine (0.42 mL, 3.0 mmol) at room temperature. The reaction mixture was heated to 80 °C for 3 h and cooled. The reaction was quenched with water, diluted with methylene chloride. The two layers were separated and the aqueous was extracted with methylene chloride. The combined organic extracts were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated. Purification by silica gel column chromatography (ethyl acetate/methanol/ammonia, 99/1/0.1) afforded 0.36 g (58%) of a solid. The free base (0.33 g, 0.80 mmol) was dissolved in 2-propanol, and precipitated with one equivalent of fumaric acid in 2-propanol to give the title compound (0.35 g, 83%) as monofumarate, 0.5 hydrate: mp 157-159 °C; $^1$H NMR (DMSO, 400 MHz), δ 1.25-1.31 (m, 2H), 1.58-1.65 (m, 3H), 2.19-2.25 (m, 2H), 2.56-2.58 (m, 2H), 2.81-2.84 (m, 2H). 3.04-3.06 (m, 2H), 4.06 (t, 2H), 4.18 (s, 4H), 6.44-7.32 (m, 7H), 10.89 (br s, 1H); MS (El) m/z 410 ($M^+$).

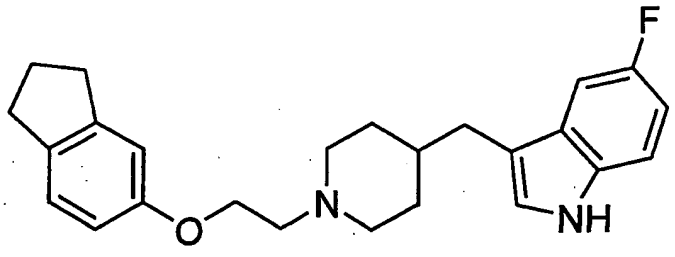
Elemental Analysis Calcd. for $C_{24}H_{27}FN_2O_3 \cdot C_4H_4O_4 \cdot 0.5H_2O$

Theory: C, 62.79; H, 6.02; N, 5.23.

Found: C, 62.61; H, 5.98.; N, 4.88.

**Example 3**

**5-Fluoro-3-{1-[2-(indan-5-yloxy)-ethyl]-piperidin-4-ylmethyl}-1*H*-indole.**



To a solution of 5-fluoro-3-[(4-piperidinyl)methyl]-1*H*-indole (0.35 g, 1.5 mmol) in DMSO (10 mL) was added 5-(2-chloroethoxy)indane (0.30 g, 1.5 mmol) followed by addition of triethylamine (0.42 mL, 3.0 mmol) at room temperature. The reaction mixture was heated to 80 °C for 3 h and cooled. The reaction was quenched with water, diluted with methylene chloride. The two layers were separated and the aqueous was extracted with methylene chloride. The combined organic extracts were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated. Purification by silica gel column (ethyl acetate/methanol/ammonia hydroxide, 99/1/0.1) afforded 0.28 g (48%) of a solid. The free base (0.25 g, 0.63 mmol) was dissolved in ethyl acetate, and precipitated with one equivalent of HCl in ether to give the title compound (0.19 g, 45%) as monohydrochloride, 0.25 hydrate: mp 150-152 °C; $^1$H NMR (DMSO, 400 MHz), δ 1.48-1.57 (m, 2H), 1.78-1.81 (m, 3H), 1.95-2.02 (m, 2H), 2.59-2.61 (m, 2H), 2.74-2.82 (m, 4H), 2.91-2.99 (m, 2H), 3.37-3.57 (m, 4H), 4.31 (t, 2H), 6.69-7.33 (m, 7H), 10.23 (br s, 1H), 11.98 (br s, 1H); MS (El) m/z 392 ($M^+$).

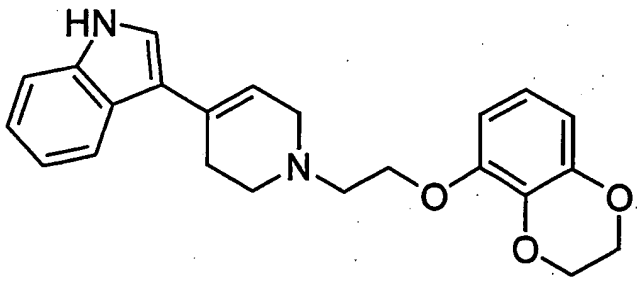
Elemental Analysis Calcd for $C_{25}H_{29}FN_2O \cdot HCl \cdot 0.25H_2O$

Theory: C, 69.27; H, 7.09; N, 6.46.

Found: C, 69.32; H, 7.08.; N, 6.32.

## Example 4

**3-{1-[2-(2,3-Dihydro-benzo[1,4]dioxan-5-yloxy)-ethyl]-1,2,3,6-tetrahydro-pyridin-4-yl}-1H-indole.**



To a solution of 5-(2-chloroethoxy)-(2,3)-dihydrobenzo[1,4]dioxan (500 mg, 2.33 mmol), 1,2,3,6-tetrahydropyridin-4-yl-1H-indole (462 mg, 2.33 mmol) and triethylamine (0.645 mL, 4.66 mmol) in DMSO (20 mL) was stirred at 80 °C overnight. The reaction mixture was cooled, quenched with $H_2O$ and diluted with EtOAc. The organic layer was washed with 3x100 mL $H_2O$, dried over $Na_2SO_4$, and concentrated. Purification by column chromatography (5% MeOH/$CH_2Cl_2$) afforded 150 mg (17%) of the title compound as a gold oil. The oxalate salt was formed by dissolving the free base in THF (20 mL) and adding oxalic acid dissolved in THF: mp 85-88 °C; $^1$H NMR (DMSO) δ 2.8 (2H, br, m), 3.46 (4H, br, m), 3.89 (2H, br, m), 4.25 (4H, m), 4.33 (2H, t), 6.17 (1H, s), 6.54 (1H, dd), 6.65 (1H, dd), 6.76 (1H, t), 7.04-7.16 (2H, m), 7.41 (1H, d), 7.52 (1H, d), 11.29 (1H, s); MS (EI) m/z 376 ($M^+$).

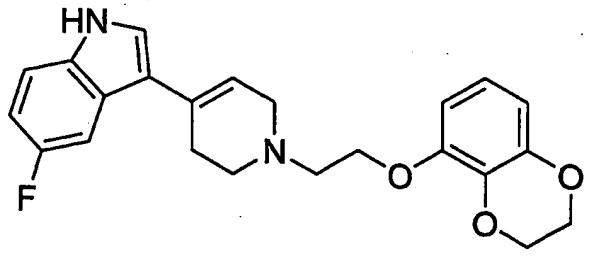
Elemental Analysis Calcd. For $C_{23}H_{24}N_2O_4 \bullet C_2H_2O_4 \bullet 0.80H_2O$

Theory: C, 62.44; H, 5.79; N, 5.82

Found: C, 62.59; H, 5.86; N, 5.42

**Example 5**

**5-Fluoro-3-{1-[2-(2,3-dihydro-benzo[1,4]dioxan-5-yloxy)-ethyl]-1,2,3,6-tetrahydro-pyridin-4-yl}-1H-indole.**




Replacing 1,2,3,6-tetrahydropyridin-4-yl-1H-indole with 5-fluoro-3-[1,2,3,6-tetrahydro-pyridin-4-yl]-1H-indole (444 mg, 2.05 mmol) in the procedure for Example 4 afforded the title compound 280 mg (61 %) as a light green oil. The

oxalate salt was prepared in EtOH to afford a yellow solid: mp 195-198 °C; $^1$H NMR (DMSO) δ 2.78 (2H, br, s), 3.45 (4H, m), 8.88 (2H, br, s), 4.26 (4H, m), 4.32 (2H, t), 6.11 (1H, s), 6.53 (1H, dd), 6.63 (1H, dd), 6.75 (1H, t), 7.4 (1H, dd), 7.50-7.57 (2H, m), 11.41 (1H, s); MS (APCI) m/z 395 $[M+H]^+$.

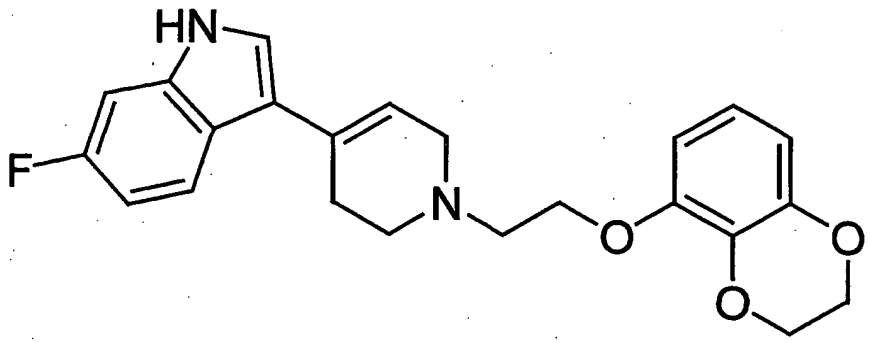
Elemental Analysis Calcd. For $C_{23}H_{23}FN_2O_4 \bullet C_2H_2O_4$

Theory: C, 61.94; H, 5.20; N, 5.78

Found: C, 61.59; H, 5.15; N, 5.94

**Example 6**

**6-Fluoro-3-{1-[2-(2,3-dihydro-benzo[1,4]dioxan-5-yloxy)-ethyl]-1,2,3,6-tetrahydro-pyridin-4-yl}-1H-indole.**




Replacing 1,2,3,6-tetrahydropyridin-4-yl-1H-indole with 6-F-3-[1,2,3,6-tetrahydropyridin-4-yl]-1H-indole (328 mg, 1.51 mmol) in the procedure for Example 4 afforded the title compound 230 mg (50%) as a viscous gold oil. The oxalate salt was prepared by adding the free base and oxalic acid in EtOH and heating to dissolve. Upon cooling to rt. crystals of the oxalate salt formed: mp 201-202 °C; $^1$H NMR (DMSO) δ 2.75 (2H, br, s), 3.44 (4H, br, s), 3.86 (2H, br, s), 4.24 (4H, m), 4.31 (2H, t), 6.15 (1H, s), 6.52 (1H, dd), 6.63 (1H, dd), 6.75 (1H, t), 6.88-6.94 (1H, m), 7.17 (1H, dd)7.50 (1H, d), 8.80-7.84 (1H, m), 11.06 (1H, s); MS (APCI) m/z 395 $[M+H]^+$.

Elemental Analysis Calcd. For $C_{23}H_{23}FN_2O_4 \bullet C_2H_2O_4$

Theory: C, 61.94; H, 5.20; N, 5.78

Found: C, 61.41; H, 5.19; N, 5.94

The results of the tests with compounds representative of this invention are given in the immediately following table.

| Example No. | Ki (nM) Serotoinn Transporter [3H]paroxetine | Ki (nM) 5-HT1A [3H]DPAT |
|---|---|---|
| 1 | 0.35 | 180 |
| 2 | 0.011 | 168 |
| 3 | 2.24 | 0 %@ 0.1 μM |
| 4 | 0.17 | 78.26 |
| 5 | 1.17 | 83.30 |
| 6 | 0.15 | 83.65 |

The compounds of this invention are useful in methods for the treatment of depression as well as other serotonin-related disorders including, but not limited to, anxiety, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, sleep disorders, sexual dysfunction, bipolar disorders, psychosis, stress-related disorders, including post-traumatic stress disorders, Tourettes' syndrome, attention deficit disorder, with and without hyperactivity, alcohol and drug addiction, Alzheimer's disease, Parkinson's disease, obesity and acute and chronic pain,

including migraine pain. Chemical dependencies and addictions which may be treated with compounds of this invention include those to opiates, benzodiazepines, cocaine, nicotine and ethanol.

The compounds herein are also useful in methods of enhancing cognition in a mammal, preferably a human, particularly in a mammal experiencing a cognitive deficit as a result of or in association with Alzheimer's disease or Parkinson's disease.

Each of these methods of treatment comprise administering a pharmaceutically effective amount of a compound of this invention, or a pharmaceutically acceptable salt thereof, to a mammal in need of such treatment or enhancement. A pharmaceutically or therapeutically effective amount of the compounds herein is understood to comprise an amount of the compound(s) in question which will obtain at least a minimum of desired effect in preventing, treating, inhibiting or managing the symptoms or causes of the malady in question. More preferably, the amount will be the minimum needed to alleviate or remove the undesirable physiological consequences of the malady in question and inhibit or prevent their re-occurrence.

This invention also provides pharmaceutical formulations comprising a pharmaceutically or therapeutically effective amount of a compound of this invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

Applicable solid carriers for pharmaceutical compositions containing the compounds of this invention can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in

the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can

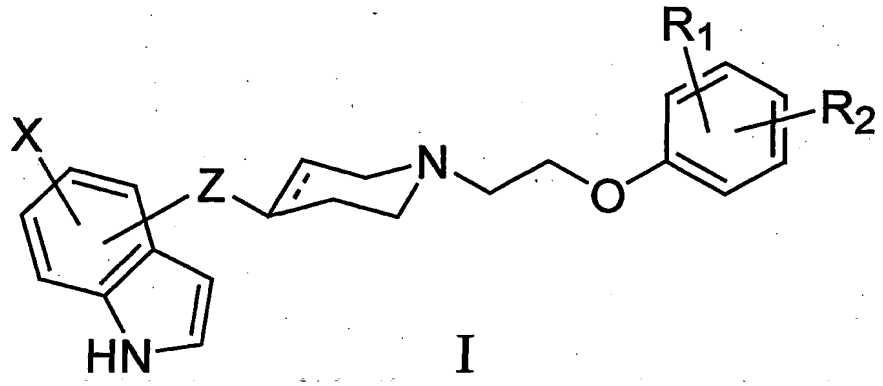
be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

The dosage to be used in the treatment of a specific psychosis must be subjectively determined by the attending physician. The variables involved include the specific psychosis and the size, age and response pattern of the patient.

The therapeutically effective amount of the compounds of this invention that is administered and the dosage regimen depends on a variety of factors, including the weight, age, sex, and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the specific compound employed, and thus may vary widely. However, it is believed that the pharmaceutical compositions may contain the compounds of this invention in the range of about 0.1 to about 2000 mg, preferably in the range of about 0.5 to about 500 mg and more preferably between about 1 and about 100 mg. Projected daily dosages of active compound are about 0.01 to about 100 mg/kg body weight. The daily dose can be conveniently administered two to four times per day.

**CLAIMS:**

1. A compound of the formula:




I

wherein:

$R_1$ and $R_2$ may each be hydrogen, alkyl of from 1 to 6 carbon atoms or alkoxy of from 1 to 6 carbon atoms; or

$R_1$ and $R_2$ may be concatenated to comprise another ring wherein the ring contains a total of 5-7 ring members;

X is selected from hydrogen, halogen, cyano, $C_1$–$C_6$ alkoxy;

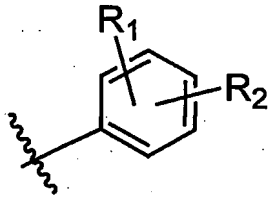
Z is $(CH_2)$n or carbonyl;

n is 0, 1 or 2;

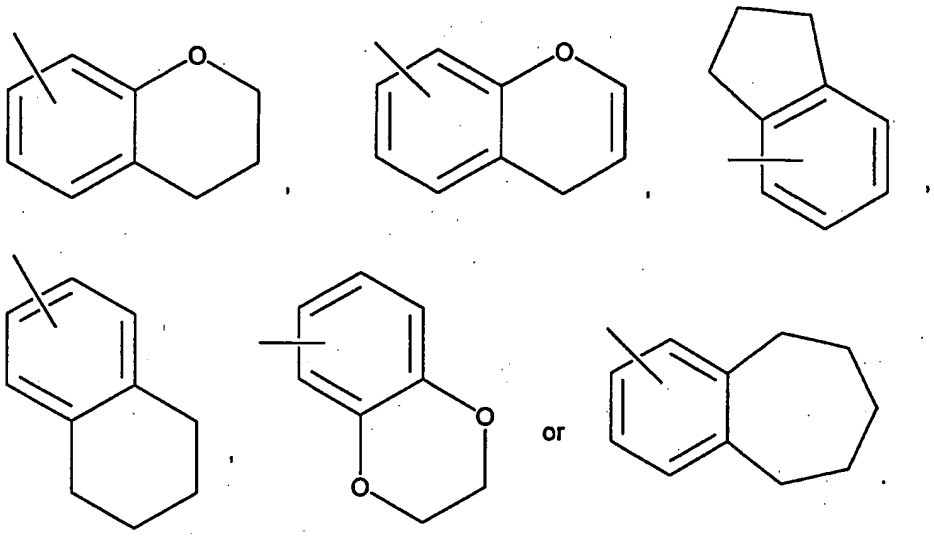
the dashed line indicates an optional double bond;

or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein the moiety:




represents a moiety selected from the group of:




3. A compound of Claim 1 wherein $R_1$ and $R_2$ are independently hydrogen, alkyl of 1 to 3 carbon atoms and alkoxy of 1 to 3 carbon atoms.

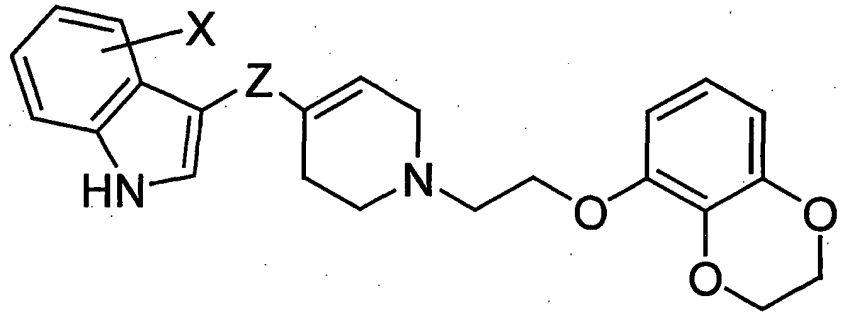
4. A compound of any one of Claims 1 to 3 wherein $R_2$, $R_3$ and $R_4$ each independently represent hydrogen, alkyl of 1 to 3 carbon atoms, chlorine or fluorine.

5. A compound of any one of Claims 1 to 4 wherein X is selected from hydrogen, fluorine, chlorine, CN and methoxy.

6. A compound of any one of Claims 1 to 5 wherein Z is a bond or $-CH_2-$.

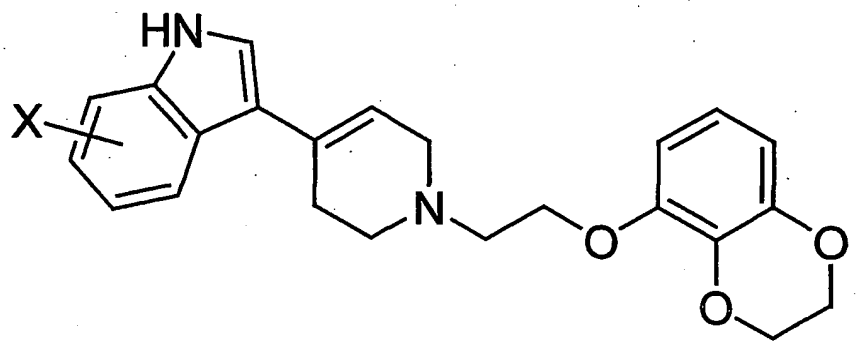
7. A compound of any one of Claims 1 to 6 wherein Z is bonded to the indole ring in the 3-position.

8. A compound of Claim 1 of the formula:



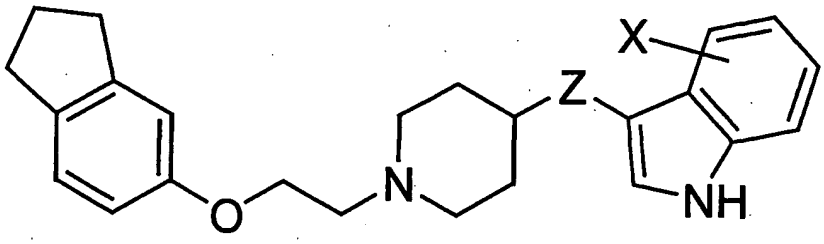

wherein X is selected from H, halogen, cyano, $C_1$–$C_6$ alkoxy; Z is $(CH_2)n$ or carbonyl;
and n is 0, 1 or 2; or a pharmaceutically acceptable salt thereof.

9. A compound of Claim 1 of the formula:




wherein X is H, halogen, cyano, $C_1$–$C_6$ alkoxy, or a pharmaceutically acceptable salt thereof.

10. A compound of Claim 1 of the formula:




wherein X is selected from H, halogen, cyano, $C_1$–$C_6$ alkoxy; Z is $(CH_2)n$ or carbonyl;
and n is 0, 1 or 2; or a pharmaceutically acceptable salt thereof.

11. A compound of any one of Claims 1 to 10 wherein the pharmaceutically acceptable salt form thereof is selected from those formed as an addition salt form from fumaric, maleic, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, oxalic, propionic, tartaric, salicyclic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene-sulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric or nitric acid.

12 A compound of Claim 1 which is 5-Fluoro-3-{1-[2-(2-methoxyphenoxy)ethyl]-piperidin-4-ylmethyl}-1*H*-indole, or a pharmaceutically acceptable salt thereof.

13. A compound of Claim 1 which is 5-Fluoro-3-{1-[2-(2,3-dihydrobenzo[1,4]dioxin-5-yloxy)ethyl]-piperidin-4-ylmethyl}-1*H*-indole, or a pharmaceutically acceptable salt thereof.

14. A compound of Claim 1 which is 5-Fluoro-3-{1-[2-(indan-5-yloxy)-ethyl]-piperidin-4-ylmethyl}-1*H*-indole, or a pharmaceutically acceptable salt thereof.

15. A compound of Claim 1 which is 3-{1-[2-(2,3-Dihydro-benzo[1,4]dioxan-5-yloxy)-ethyl]-1,2,3,6-tetrahydro-pyridin-4-yl}-1H-indole, or a pharmaceutically acceptable salt thereof.

16. A compound of Claim 1 which is 5-Fluoro-3-{1-[2-(2,3-dihydro-benzo[1,4]dioxan-5-yloxy)-ethyl]-1,2,3,6-tetrahydro-pyridin-4-yl}-1H-indole, or a pharmaceutically acceptable salt thereof.

17. A compound of Claim 1 which is 6-Fluoro-3-{1-[2-(2,3-dihydro-benzo[1,4]dioxan-5-yloxy)-ethyl]-1,2,3,6-tetrahydro-pyridin-4-yl}-1H-indole, or a pharmaceutically acceptable salt thereof.

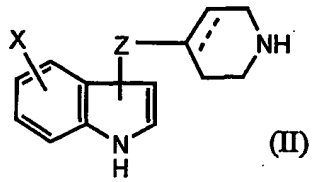
18. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

19. A method of treating depression in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof.

21. A method of treating anxiety in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof.

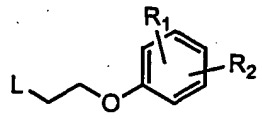
22. A process for preparing a compound of formula (I) which comprises:

a) reacting a compound of formula




(II)

wherein X and Z are as defined above, with a compound of formula:




wherein $R_1$ and $R_2$ are as defined herein and L is a leaving group,
or

b) converting a basic compound of formula I to a an acid addition salt or vice versa

or

c) isolating an isomer of a compound of formula I from a mixture of isomers.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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20 June 2002 (20.06.2002)

PCT

(10) International Publication Number
WO 02/048105 A3

(51) International Patent Classification[7]: C07D 209/32, 319/18, 401/06, 405/14, A61P 25/00, A61K 31/44 // (C07D 401/06, 211:00, 209:00) (C07D 405/14, 319:00, 211:00, 209:00)

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(74) Agents: MAZZARESE, Joseph, M.; American Home Products Corporation, Patent Law Dept., Five Giralda Farms, Madison, NJ 07940 et al. (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

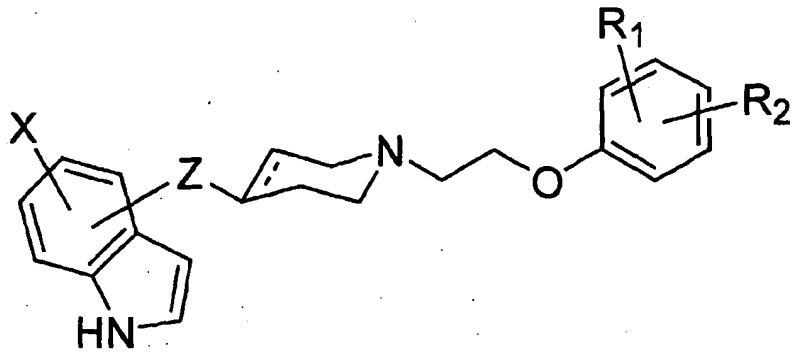
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
31 October 2002

*[Continued on next page]*

(54) Title: ARYLOXY PIPERIDINYL DERIVATIVES FOR THE TREATMENT OF DEPRESSION




(I)

(57) Abstract: This invention provides compounds useful in treating serotonin-related central nervous system disorders, including anxiety, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, sleep disorders, sexual dysfunction, alcohol and drug addiction, Alzheimer's disease, Parkinson's disease, obesity and migraine, the compounds having the general formula: wherein: $R_1$ and $R_2$ may each be H or an alkyl or alkoxy group; or $R_1$ and $R_2$ may be concatenated to form a bicyclic ring system with the phenyl ring to which they are bound; X is selected from hydrogen, halogen, cyano, $C_1$-$C_6$ alkoxy; Z is $(CH_2)n$ or carbonyl; n is 0, 1 or 2; the dashed line indicates an optional double bond; or a pharmaceutically acceptable salt thereof.

WO 02/048105 A3

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/50882

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/32 C07D319/18 C07D401/06 C07D405/14 A61P25/00 A61K31/44 //(C07D401/06,211:00,209:00),(C07D405/14,319:00, 211:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EP 0 714 894 A (LILLY, ELI, AND CO., USA) 5 June 1996 (1996-06-05) cited in the application page 5, line 1 - line 11; examples 37,40 page 25, line 3 - line 9 --- | 1,3-7, 11,18,22 |
| X | EP 0 169 148 A (ROUSSEL-UCLAF, FR.) 22 January 1986 (1986-01-22) page 9, line 11 - line 15; example 28 --- | 1 |
| Y | WO 99 55697 A (AMERICAN HOME PRODUCTS CORPORATION, USA) 4 November 1999 (1999-11-04) page 5, line 11 - line 22; examples 5-7 --- -/-- | 1,18,19, 21 |

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 4 July 2002 | 15/07/2002 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Bakboord, J |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Interna[redacted]nal Application No
PCT/US 01/50882

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 99 05140 A (MIKKELSEN IVAN ;LUNDBECK & CO AS H (DK); MOLTZEN EJNER KNUD (DK);) 4 February 1999 (1999-02-04) examples | 1,18,19, 21 |
| Y | MALLERON J-L ET AL: "NEW INDOLE DERIVATIVES AS POTENT AND SELECTIVE SEROTONIN UPTAKE INHIBITORS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 36, no. 9, 1993, pages 1194-1202, XP000195950 ISSN: 0022-2623 cited in the application tables I,II | 1,19,21 |
| Y | WO 99 55672 A (AMERICAN HOME PROD) 4 November 1999 (1999-11-04) claim 1 | 1,18,19, 21 |
| P,Y | WO 01 49680 A (H. LUNDBECK A/S, DEN.) 12 July 2001 (2001-07-12) claim 1 | 1,18,19, 21 |
| P,Y | WO 01 043740 A (BRISTOL-MYERS SQUIBB CO., USA) 21 June 2001 (2001-06-21) claim 1 | 1,18,19, 21 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/50882

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19 and 21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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International Application No
PCT/US 01/50882

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